bio-protocol Preprint

Not Peer Reviewed
Ask a question online

Modeling Study design

Sixue Zhang

Updated date: May 19, 2020

An abbreviated version of this protocol was published in Science Translational Medicine in Jan 2020

β-amyloid redirects norepinephrine signaling to activate the pathogenic GSK3β/tau cascade

DOI: 10.1126/scitranslmed.aay6931

Detailed protocol

Protocol of computational modeling of Aβ_{42} and α_{2A}AR

Dr. Sixue Zhang, Chemistry Department, Drug Discovery Division, Southern Research, USA

Use Schrödinger Small Molecule Drug Discovery Suite (Schrödinger LLC, New York, NY) for homology model building as well as docking of Aβ_{42} and α_{2A}AR.

Building homology model of α_{2A}AR

Download the sequence of human α_{2A}AR from UniProt database (https://www.uniprot.org/) with UniProt ID P08913.
Download the crystal structure of human adrenergic receptor β_2 from PDB database (https://www.rcsb.org/) with PDB ID 3PDS.
Use Schrödinger Maestro to delete irrelevant parts in the β_2AR crystal structure and only retain residue 29 to 342.
Follow the default Schrödinger homology model building procedures, use α_{2A}AR sequence as the inquiry sequence and β_2AR residue 29 to 342 as the template to build the human α_{2A}AR homology model.

Building homology model of Aβ_{42} pentamer

Download the NMR structure of Aβ_{42} from PDB database with PDB ID 1Z0Q.
Choose the first NMR entry as the 3D structure of Aβ_{42} for subsequent procedures
Use Schrödinger Protein Preparation Wizard to prepare the raw structure, minimize hydrogen atoms only
Use the dimer option in Schrödinger PIPER module to dock two prepared Aβ_{42} monomers to make a dimer. Criterion for choosing the best dimer conformation: residues 39 to 42 from each monomer must be in contact with each other.
Use the trimer option in Schrödinger PIPER module to dock three prepared Aβ_{42} monomers to make a trimer. Criterion for choosing the best trimer conformation: residues 39 to 42 from each monomer must be in contact with each other.
Use the receptor/ligand option in Schrödinger PIPER module to dock the previously generated dimer (as the ligand) to the trimer (as the receptor) to make the pentamer, use the characters of Aβ_{42} pentamer described in the literature (Tran, L.; *et. al. Sci. Rep.* 2016, 6: 21429) as guidelines to choose the best generated pentamer conformation. Namely, residues 39 to 42 from each monomer form a hydrophobic core, overall shape is disc-like, and the angles between each of the five arms are relatively even.

Docking Aβ_{42} onto α_{2A}AR

Use the receptor/ligand option in Schrödinger PIPER module to dock previously generated Aβ_{42} pentamer (as the ligand) to α_{2A}AR homology model (as the receptor). Choose type “repulsion” as the constraint for the residues of α_{2A}AR in the transmembrane region and intracellular region to ensure Aβ_{42} pentamer is only docked to the extracellular region of α_{2A}AR. Criterion for choosing the best docked complex conformation: no part of Aβ_{42} pentamer intrudes into the transmembrane region.
Use Schrödinger Prime to perform a geometry optimization on the residues within the contact region between Aβ_{42} and α_{2A}AR to eliminate any atom clash.

How to cite:(Readers should cite both the Bio-protocol preprint and the original research article where this protocol was used)

1. Zhang, S. (2020). Modeling Study design. Bio-protocol Preprint. bio-protocol.org/prep318.
2. Zhang, F., Gannon, M., Chen, Y., Yan, S., Zhang, S., Feng, W., Tao, J., Sha, B., Liu, Z., Saito, T., Saido, T., Keene, C. D., Jiao, K., Roberson, E. D., Xu, H. and Wang, Q.(2020). β-amyloid redirects norepinephrine signaling to activate the pathogenic GSK3β/tau cascade . Science Translational

Medicine 12(526). DOI: 10.1126/scitranslmed.aay6931